UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,498	02/15/2000	HANS-PETER SCHWARZ	BHV-314.01	8060

7590 06/04/2002

TOWNSEND AND TOWNSEND AND CREW LLP
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	16

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/424,498	Applicant(s) SCHWARZ ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- *The MAILING DATE of this communication appears n the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *31,32,35-37,39-41 and 43-71* is/are pending in the application.

4a) Of the above claim(s) *45-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *31,32,35-37,39-41,43,44 and 64-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

The Amendment and Response filed March 4, 2002 (Paper No. 15) has been entered. Claims 33, 34, and 38 have been cancelled and Claims 64-71 have been added. Claims 31, 32, 35, 36, 37, 39, 40, 41, and 43-71 are pending, Claims 45-63 are withdrawn as being drawn to a non-elected invention and Claims 31, 32, 35, 36, 37, 39, 40, 41, 43-44, and 64-71 will be considered in this Office Action.

Information Disclosure Statement

References AC, and AN of he Information Disclosure Statement filed March 29, 2000 (Paper No. 6) have been considered as indicated on the Form 1449, a copy of which is attached to this Office Action. References AD-AL have been considered as to the information provided in references AA-AK of Paper No. 9 which Applicants indicate are the corresponding references.

Objections

The objection of Claims 31-42 and 44 is withdrawn in light of the amendment to Claim 31 adding the full name "von Willebrand Factor".

The objection of Claim 45 is maintained. Claim 45, an independent claim, has not been amended and still refers to a vWF propeptide. As stated in the previous Office Action, this protein would be more accurately identified by its full name "von Willebrand Factor". This objection would be overcome by adding the full name of the protein in

front of the acronym in parenthesis in all of the independent claims as follows: "von Willebrand Factor (vWF) propeptide...".

The objection of Claim 44 as objected to under 37 CFR 1.75 as being a substantial duplicate of claim 34 is withdrawn in light of the cancellation of Claim 34.

Rejections Withdrawn

The rejection of Claim 33, and Claims 34 and 38 dependent there from, under 35 U.S.C. 112, second paragraph as unclear as to what is meant by the phrase "comprising pro-vWF, said pro-vWF containing said vWF propeptide is withdrawn in light of the cancellation of Claims 33, 34, and 38.

The rejection of Claim 37 under 35 U.S.C. 112, second paragraph as improperly containing the trademark/trade name FEIBA (Immuno AG) is withdrawn in light of the amendment to the claim.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of Claims 32, 37, and 38 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Applicants argument that the meaning of the term "consisting essentially of" is clear is not persuasive because Claim 32 recites "*essentially comprised of*" (emphasis added) and not "consisting essentially of". Therefore, as stated in the previous Office Action:

The transitional phrase, "essentially comprised of" in Claim 32 is unclear as to the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. The transitional term "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps whereas the transitional term "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention (see MPEP 2111.02). Clarification as to the scope of the claim is required. For the purposes of the present Office Action, the claim will be given its broadest interpretation (i.e. "comprising").

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-32, 35-37, 39-40, 43-44, and new claims 64-71 are rejected under 35 U.S.C. 102(b) as being anticipated by Burnouf-Radosevich et al. (U.S. Patent No. 5,408,039, 1995). It is noted that the references of Turecek et al., Ruggeri et al., and

Wise et al. are used as evidence for inherent properties of the preparation of Burnouf-Radosevich et al. in response to Applicants arguments. However, the Burnouf-Radosevich et al. reference alone meets all of the limitations of the claims.

A response to Applicant's arguments is provided after the following review of the Burnouf-Radosevich et al. teachings as stated in the previous Office Action. Burnouf-Radosevich et al. teach that pharmaceutical compositions comprising vWF from vWF-enriched plasma derivatives are very well known in the art (Col. 1-Col. 2). Burnouf-Radosevich et al. disclose a highly purified vWF concentrate that is subjected to a solvent-detergent treatment known for its efficiency in destroying lipid enveloped viruses (Col. 5, Example and "Viral Inactivation Treatment"). The vWF is synthesized as a pre-pro-peptide. Upon cleavage of the signal peptide, the pro-vWF (containing the propeptide and mature peptide segments) dimerizes, assembles into multimers, and then the propolypeptide (741 aa segment) is removed by proteolytic cleavage. However, cleavage is not always complete. Therefore, it appears that a vWF plasma derivative, such as disclosed in Burnouf-Radosevich et al. would comprise the vWF pro polypeptide, the pro-vWF, as well as the mature vWF. In addition, Burnouf-Radosevich et al. teach that the composition disclosed therein may also comprise Factor VIII (Col. 5, lines 55-60). Therefore, the claims appear to be anticipated by Burnouf-Radosevich et al.

Newly added Claim 67 (composition comprising the pro-vWF) is also rejected for the same reasons applied above. Claim 68 is rejected because the fact that pro-vWF is recombinant does not patentably distinguish the composition over that of the prior art

since both recombinant and isolated forms of pro-vWF would have the same sequence, structure, and function. Claim 69 is rejected for the reasons stated above. It is known that the propeptide (741 aa segment) is required for factor VIII binding either as part of the pro-vWF or in trans as the propeptide. Thus, since Burnouf-Radosevich et al. teach that the composition may also comprise Factor VIII (Col. 5, lines 55-60) and since this composition maintains Factor VIII and vWF activity (see Col. 5, lines 64-66), it would be inherent that the pro-vWF complexed to the factor VIII.

Applicant's argue that the rejection fails to show that vWF propeptide is necessarily present in the compositions discussed in Burnouf et al. and thus Burnouf et al. fail to anticipate the claimed invention. Applicants argue that the composition of Burnouf et al. is prepared from plasma and would not contain the vWF propeptide because the propeptide subunit is cleaved from the multimeric form of vWF before it is released from intracellular storage sites into circulation. This argument has been considered but is not deemed to be persuasive for the following reasons. While some of the propeptide subunit is cleaved from vWF intracellularly, Turecek et al. (Blood (1999) 94(5): 1637-1647) and Ruggeri et al. (Thrombosis and Haemostasis (1992) 67(6): 594-599) provide evidence that vWF released from endothelial cells contains incompletely processed pro-vWF and Turecek et al. show that propeptide cleavage from unprocessed vWF occurs extracellularly in the circulation (see abstract).Wise et al. state that the vWF propeptide is cleaved and secreted as a distinct protein (see Cell (1988) 52: 229-236; p. 229, Col. 2, lines 6-8). Thus, absent evidence to the contrary,

the composition of Burnouf et al. would necessarily contain the pro-vWF and vWF propeptide that was processed extracellularly.

Applicant's argue that there is no evidence that pro-vWF or vWF propeptide would remain in solution following centrifugation and aluminum hydroxide purification steps which precede formation of the Burnouf et al. composition. This argument has been considered but is not deemed persuasive for the following reasons. It appears that because the propeptide (or the propeptide of the pro-vWF) covalently binds to the multimer complex (via disulfide bonding) that the propeptide would remain in solution following centrifugation and aluminum hydroxide purification. Wise et al. show that when free propeptide and mature vWF are cotransfected into cells, both the propeptide and mature vWF precipitated with anti-vWF antiserum which recognizes only the mature vWF. Both the propeptide and mature vWF also precipitate with monoclonal antibody specific for the propeptide. Wise et al. also state that dissociation of the vWF propeptide from the mature vWF was only achieved upon reduction with 2-mecaptoethanol in SDS and therefore conclude that the propeptide and mature vWF are covalently associated (see p. 233, Col. 2 and Figure 6B). Thus, absent any evidence that the Burnouf-Radosevich et al. method involves a step to specifically eliminate the propeptide from the composition isolated therein, it appears that the Burnouf-Radosevich et al. preparation contains the vWF propeptide. In addition, Wise et al. indicate that propeptide cleavage is not required fro secretion or multimer formation. Wise et al. state that multimers can be assembled from uncleaved pro-vWF and that uncleaved pro-vWF are present in multimers from endothelial cell culture

medium and circulating in vivo (p. 231, section bridging Col. 1 and 2). Ruggeri et al. (Thromb. Haem. (1992) 67(6) 594-599) also state that a certain proportion of normal plasma vWF multimers contain pro-vWF peptide that are secreted from endothelial cells by the constitutive pathway (see p. 594, Col. 2, lines 16-20).

Claims 31-32, 39-40, 43-44, and 64-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-1020; ref. AY of IDS of Paper No. 6) is maintained.

(Previous Rejection) As stated in the previous Office Action, Takagi et al. disclose a composition comprising vWF propeptide isolated from human platelets (see p, 6017, Experimental Procedures). Since the vWF propeptide is a glycoprotein isolated from platelets it is considered a platelet glycoprotein component (clms 39-40).

The present claims are drawn to a product-by-process. As evidenced by the prior art, it appears that the vWF propeptide was very well known in the art at the time of the invention. While the vWF propeptide composition of the prior art appears to have been made by a process different than that claimed, the vWF propeptide known in the art is identical in structure and function to the presently claimed polypeptide and would inherently have the same properties and utilities as the polypeptide presently claimed. Applicants are reminded that something which is old does not become patentable upon the discovery of a new use. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977) (see

MPEP 2112). In the present case, it appears that the claimed compositions are patentably indistinguishable from the prior art. In the alternative, the claimed compositions would be obvious over the prior art as described in the obviousness rejection below.

(Response to Arguments) Applicants argue that that the Takagi et al. reference does not meet the limitations of the claims because the composition disclosed therein has not been "treated for at least one of virus inactivation and virus removal". This argument has been considered but is not deemed to be persuasive. As stated previously, the present claims are product by process claims wherein the composition has been treated for virus removal. The specification does not indicate the extent of the virus removal. The claim is interpreted to mean that some viruses are removed in the process of making the composition. Takagi et al. teach several steps in the purification of the vWF propeptide that would necessarily inactivate or remove at least some viruses. Many viruses would be removed in the isolation of the propeptide from platelets (which involves sonication and centrifugation). The Takagi et al. purification involves affinity purification on a collagen column, passage over a organomercurial-agarose column, and then a lentil lectin agarose column (see p. 6017, Col. 2, 1st paragraph of Exptl. Procedures). In the first step of this purification process alone many of the viruses would be removed since column binding would require protein affinity for collagen. Finally, the absence of contaminating proteins from viruses is confirmed in the SDS-PAGE gel shown in Figure 1 (p. 6018). Thus, absent evidence to the contrary,

it appears that the Takagi et al. propeptide composition is patentably indistinguishable from the claimed vWF propeptide composition. And, the rejection is maintained.

New Claims 64-66 have been added to this rejection. Claims 64 and 65 are drawn to the vWF propeptide preparation wherein the vWF propeptide is 90% or 95% pure. The present Specification does not describe a method of purifying the vWF propeptide but only points to the prior art including Takagi et al. stating that "[t]he preparation of pp-vWF or pro-vWF is well known in the art" (see p. 4, last paragraph of Specification). Thus, it appears that the purification processes described in Takagi et al. would provide a vWF propeptide which is at least 90% or 95% pure. Claim 66 adds that the preparation comprises at least two components selected from the group consisting of a blood factor, a platelet component, and a phospholipid. The assays performed with the propeptide preparation of Takagi et al. involve combining the vWF propeptide with platelet rich plasma (see p. 6017, Col. 2, "Platelet Aggregation"). Thus, the Takagi et al. compositions are considered to contain the vWF propeptide and platelet components.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31, 32, 35, 36, 37, 39, 40, 43, 44, and newly added Claims 64-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leyte et al. (Biochem. J. (1991) 274: 257-261; ref. AW in IDS of Paper No. 6) and Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-1020; ref. AY of IDS of Paper No. 6) in view of Burnouf-Radosevich et al. (U.S. Patent No. 5,408,039, 1995) and Wise et al. (Cell (1988) 52: 229-236). A response to Applicants arguments will follow the rejection.

Rejection: Leyte et al. teach that the formation of a complex between Factor VIII and vWF is important in the maintenance of normal haemostasis and that some patients suffer from bleeding disorders associated with aberrant interaction between Factor VIII and vWF (p. 257, Col. 2, lines 1-7). Leyte et al. teach the purification of vWF propolypeptide (p. 258-259) and discuss experiments that lead to the conclusion that the propolypeptide is essential in the post-translational processes that lead to the expression of a functional Factor VIII binding site on the mature vWF subunit (see abstract). Leyte et al. also teach that the propolypeptide sequence was well known and

could be produced recombinantly using procedures well known in the art (p. 258, Materials and Methods).

Leyte et al. do not teach that the purified vWF propolypeptide has been treated for at least one of virus inactivation or virus removal.

As discussed above, Takagi et al. disclose a composition comprising vWF propolypeptide isolated from human platelets (see p, 6017, Experimental Procedures). Since the vWF propolypeptide is a glycoprotein isolated from platelets it is considered a platelet glycoprotein component (clms 39-40).

Takagi et al. do not teach that the purified vWF propolypeptide has been treated for at least one of virus inactivation or virus removal. However, as mentioned above, the purification steps of Takagi et al. would inherently inactivate or remove at least some of the viruses found in the original platelet concentrate.

Burnouf-Radosevich et al. teach that viral inactivation of solutions containing vWF were known in the art at the time of the invention (Col. 5, lines 55-60). Burnouf-Radosevich et al. also teach vWF compositions that are used in methods of treatment and contain Factor VIII.

Wise et al. teach that the larger vWF multimers are the most active in promoting adhesion of platelets to the subendothelium following vascular surgery (p. 229, col. 2, lines 23-26). Wise et al. show that the interaction between the propeptide and mature vWF that leads to the formation of assembled multimers can occur both before and after propeptide cleavage (p. 234, Col. 1, second full paragraph). Wise et al. also teach that mutation of the propeptide could lead to variant forms of von Willebrand disease that

are characterized by reduction or absence of large multimers in the plasma (p. 234, Col. 2, lines 5-9).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to make a composition comprising the vWF propeptide or the pro-vWF as was well known and taught in Leyte et al., Takagi et al., Burnouf-Radosevich et al. and Wise et al. (see Table 1, pMT2-vWF-KKS expressing the uncleaved pro-vWF) and treat the composition for virus inactivation or removal as taught in Burnouf-Radosevich et al. One of ordinary skill would have been motivated to do so because virus inactivation or virus elimination would make a safer composition for administration to patients. One of ordinary skill would have been motivated and had a reasonable expectation of success in administering pro-vWF and the propeptide to patients with the teachings of Leyte et al. and Wise et al. in hand. Leyte et al. teach that the vWF propeptide is essential for the expression of a functional Factor VIII binding site and that complex formation between Factor VIII and vWF is essential to maintain haemostasis. Wise et al. state "A disruption of this process by mutation in the propeptide could lead to some of the variant forms of von Willebrand disease that are characterized by a reduction or absence of large multimers in the plasma" (p. 234, Col. 2, lines 5-9). One of ordinary skill would have quickly recognized from Wise et al. that one way to treat a disease caused by reduction or absence of large multimers in the plasma would be to administer the peptide essential for forming these large multimers. In the present case, Wise et al. show that the peptide essential for forming the large multimers is the propeptide, either in its pro-vWF form or in trans as the separate propeptide. Thus,

with Leyte et al. and Wise et al. in hand one of ordinary skill would have recognized the importance of the pro-vWF and propeptide of vWF in maintaining haemostasis and in replacement of the larger multimers known to be more active in blood clotting.

This rejection also applies to newly added Claims 64-71. Claims 64-65 and 70-71 are drawn to preparations wherein either the vWF propeptide is 90% or 95% pure of the pro-vWF is 90%-95% pure. The present Specification does not describe a method of purifying either the vWF propeptide or the pro-vWF but only points to the prior art including Takagi et al. and Leyte et al. stating that "[t]he preparation of pp-vWF or pro-vWF is well known in the art" (see p. 4, last paragraph of Specification). Thus, it appears that the purification processes described in Takagi et al. and Leyte et al. would provide pro-vWF and vWF propeptide which are at least 90% or 95% pure.

Response to Arguments: Applicants arguments have been considered but are not deemed persuasive for the following reasons:

The argument that there is no discussion in Leyte et al. regarding the activity of vWF propeptide per se, i.e., the vWF propeptide itself, rather than as a component of the larger immature vWF is not persuasive for the following reasons. As indicated by Applicants (see Response of Paper No. 15, p. 8), the vWF-propeptide, propeptide of vWF, the propolypeptide of vWF, and the pp-vWF all refer to the 741 amino acid propeptide segment of vWF. Thus, the examiner interprets the statement "the pro-polypeptide also directs the folding and disulfide-bond formation within the N-terminus of mature vWF required for Factor VIII binding" (Leyte et al. p. 261, Col. 1, last line of

Discussion) to refer to the 741 amino acid polypeptide and not the larger immature vWF.

Applicants argument that Leyte et al. notes that the potential role ascribed to vWF propeptide is simply a proposal and only provides an obvious to try rationale is not persuasive. First, it appears that applicant is making the argument based on the Leyte et al. reference alone. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Second, one of the three basic criteria for obviousness is that there must be a reasonable expectation of success. In view of the results of the Leyte et al. reference, which shows that the propeptide is involved in both vWF multimerization and Factor VIII binding (see p. 261, Col. 1, last lines of Discussion) and what was known in the prior art at the time of the invention, it appears that one of skill in the art at the time of the invention, with the Leyte et al., Takagi et al., Burnouf-Radosevich et al., and Wise et al. references in hand, would have had a reasonable expectation of success that a composition comprising the vWF pro-vWF or the propeptide of vWF, as was well known and taught in Leyte et al.,Takagi et al., Burnouf-Radosevich et al. and Wise et al., could be treated for virus inactivation or removal as taught in Burnouf-Radosevich et al. and successfully used in treatments of patients suffering from bleeding disorders associated with an aberrant interaction between factor VIII and structurally defective vWF since both Leyte et al. and Wise et al. teach the (see Leyte et al. p. 257, Col. 2, lines 3-7). Thus, as stated above, with Leyte et al. and Wise

et al. in hand one of ordinary skill would have recognized that the propeptide, either in its pro-vWF form or in trans as the separate propeptide is essential for forming the most active large multimers and thus, one successful approach to treat a disease caused by reduction or absence of large multimers in the plasma would be to administer this peptide essential for forming these large multimers especially in instances wherein mutation of the propeptide leads to the disease (see Wise et al. p. 234, Col. 2, lines 5-10). Thus, the rejection is maintained.

Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Leyte et al. (Biochem. J. (1991) 274: 257-261; ref. AW in IDS of Paper No. 6),Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-1020; ref. AY of IDS of Paper No. 6), and Burnouf-Radosevich et al. (U.S. Patent No. 5,408,039, 1995) as applied to claims 31, 32, 35, 36, 37, 39, 40, 43, 44, and 64-71 above, and further in view of Kaufman (U.S. Patent No. 5,198,349, 1993).

Applicants argue that the fact that the fact that phospholipids are useful to stabilize Factor VIII provides no motivation to utilize phospholipids with completely different proteins. This argument has been considered but is not deemed persuasive for the following reasons.

The rejection did not state that the phospholipids were added to the composition to stabilize vWF but to make a more stabilizing solution for combining with Factor VIII as taught in Kaufmann et al. (see rejection repeated below). If Applicant is implying that the motivation is not sufficient because it is not the same as that of the present

invention, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Thus, the rejection is maintained. The rejection is repeated below.

The teachings of Leyte et al., Takagi et al. and Burnouf-Radosevich et al. have been described above. As discussed above, Burnouf-Radosevich et al. teach that coagulation diseases are treated with compositions comprising both vWF and Factor VIII (Col. 1, lines 45-50).

Leyte et al., Takagi et al. and Burnouf-Radosevich et al. do not teach that the compositions disclosed therein contain phospholipids.

Kaufman teach that phospholipids stabilize Factor VIII and disclose compositions containing vWF and stabilizing phospholipids (Col. 2, lines 13-15 and 35-37).

Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention, to add phospholipids to a composition comprising vWF because compositions of vWF and Factor VIII are known to be used in treating coagulation disorders (see Burnouf-Radosevich et al.) and, as taught in Kaufman, it was well known in the art that phospholipids act as stabilizers of Factor VIII. One of ordinary skill in the art would have been motivated to add phospholipids to a composition of vWF to make a more stabilizing solution for combining with Factor VIII as has been done in Kaufman et al. Therefore, it appears that the claims are unpatentable over the prior art.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
June 3, 2002

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER